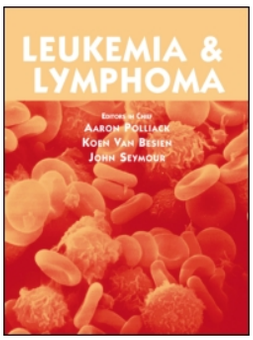

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ORIGINAL ARTICLE

Stable pulmonary function after haploidentical stem cell transplantation with post-transplant cyclophosphamide: a single center experience

Annalisa Paviglianiti[a,b], Simona Sestili[a], Antonio Bianchessi[a,c], Mara Memoli[a,d], Remy Dulery[a], Anne Banet[a], Zoe Van De Wyngaert[a], Ramdane Belhocine[a], Tounes Ledraa[a], Florent Malard[a], Mohamad Mohty[a] and Eolia Brissot[a]

[a]Sorbonne University, Service d'Hématologie Clinique et Thérapie cellulaire, Hôpital Saint-Antoine, Paris, France; [b]University Campus Bio-Medico, Rome, Italy; [c]Department of Molecular Medicine, University of Pavia and Division of Hematology, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; [d]Department of Medicine and Surgery, Hematology and Hematopoietic Stem Cell Transplant Center, University of Naples Federico II, Naples, Italy

ABSTRACT

Prior studies have reported pulmonary function tests (PFT) before and after related and unrelated allogeneic hematopoietic stem cell transplantation (HSCT). However, limited data exist on the evaluation of lung function after haploidentical stem cell transplantation (HAPLO) with post-transplant cyclophosphamide (PTCY). We retrospectively reported the evaluation of PFTs at screening before HAPLO in 80 patients at 100 days and 1 year of follow-up. The proportion of surviving patients with available PFTs at 100 days and 1 year were 86% and 68%, respectively. During the follow-up period, four patients met the criteria for bronchiolitis obliterans syndrome and two for interstitial lung disease. Overall survival was 73% (95% CI 62–82%) at 2 years. We observed a significant reduction in diffusing capacity of the lungs for carbon monoxide (DLCO) corrected for the most recent hemoglobin concentration (DLCOc) at 100 days after HAPLO. However, an overall substantial stable pulmonary function was observed at 1 year.

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KEYWORDS
PFT; HAPLO; pulmonary function; pulmonary function tests; HSCT; lung function score

Introduction

Allogeneic hematopoietic stem cell transplantation (HSCT) is a curative treatment option for hematological malignancies [1]. However, its use is limited by the development of serious complications. Recent advances in the preparative regimens and post-HSCT supportive care have contributed to improve survival [2]. Nevertheless, pulmonary complications occur in more than 30% of patients after HSCT [3]. Therefore, lung function is routinely checked by means of pulmonary function tests (PFT) in the pre-HSCT setting. Pre-transplant PFT are useful tools providing baseline measurements and aid in diagnosing underlying respiratory abnormalities at pre-HSCT screening.

Lung dysfunction before HSCT has been reported as a risk factor for both pulmonary morbidity and mortality [4,5]. Several retrospective studies have described the impact of PFT on outcomes in HSCT recipients in the setting of related and unrelated donor type [6–10]. However, limited data exist on the evaluation of PFT after haploidentical stem cell transplantation (HAPLO). In the last few decades, the use of HAPLO with post-transplant cyclophosphamide (PTCY) has progressively increased. Nonetheless, very few studies have reported PFT evaluation including HAPLO as graft source in the adult [11] and pediatric [12] setting, with a limited number of HAPLO recipients described in their cohorts. Furthermore, at the time of these reports, T-cell depletion was not conducted with PTCY as it had not been introduced in everyday clinical practice.

We here describe the pulmonary function trend in a uniform cohort of patients undergoing HAPLO with PTCY.

Methods

Study design

We retrospectively analyzed 80 adult patients who underwent HAPLO with PTCY and low dose antithymocyte globulin (ATG) between 2013 and 2019 at Saint Antoine Hospital, Paris, France. All patients with available pre- and post-transplant PFT results were

CONTACT Annalisa Paviglianiti annalisa.paviglianiti@gmail.com Sorbonne University, Service d'Hématologie Clinique et Thérapie cellulaire, Hopital Saint Antoine, 184, rue du Faubourg Saint Antoine, Paris 75012, France

included in the study. Patients who underwent any prior allogeneic HSCT were excluded. The conditioning regimen was classified as myeloablative (MAC) if containing intravenous busulfan at the total dose of 9.6 mg/kg of intravenous busulfan (3.2 mg/kg/day for three days) [13]. Sequential conditioning was defined as a short course of intensive chemotherapy followed by a reduced intensity conditioning (RIC). Other conditioning regimens were considered as RIC [13]. Stem cell source was unmanipulated peripheral blood stem cells (PBSC) or bone marrow (BM). Patients were stratified according to the disease risk index (DRI) [14]. Graft-versus-host disease (GvHD) prophylaxis consisted of cyclosporine A, initiated on day +6 at a dose of 3 mg/kg daily in continuous infusion and mycophenolate mofetil (MMF) at a dose of 45 mg/kg daily, divided into 2 intakes from day +6 until day +35. High dose (50 mg/kg) PTCY was administered on days +3 and +4, or days +3 and +5 in all but 9 patients, who received it on day +3 only, because of toxicity. Patients received rabbit ATG at a dose of 2.5 mg/kg on days −3 and −2, or only on day −3, except for 7 patients who did not receive ATG because of toxicity. All patients who proceeded to HAPLO provided written informed consent for the use of their data for clinical research, in accordance with the modified guidelines of the Declaration of Helsinki and the local ethics committee. The Saint Antoine Institutional Review Board approved the study.

Pulmonary function tests

PFTs were performed at baseline (screening for HAPLO), 100 days, and 1 year. All PFT values were expressed as a percentage of predicted values in healthy controls matched for age and gender, except for forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio. Diffusing capacity of the lungs for carbon monoxide (DLCO) measurements were corrected for the most recent hemoglobin concentration (DLCOc). Among patients who received a bronchodilator challenge during the PFT, only the pre-bronchodilator values were used. All PFTs were performed in the same laboratory at Hospital Saint Antoine, Paris.

Definitions of pulmonary function abnormalities and lung function score

Restrictive lung disease was defined as a total lung capacity (TLC) <80% of the predicted value. A value of TLC from 79% to 70% was graded as mild, from 69% to 60% as moderate, moderately severe at 59% to 50% and severe if <50%. An abnormal DLCOc was considered as having <80% of the predicted value and graded as mild from 79% to 60%, moderate from 59% to 40%, and severe if < 40%. Airflow obstructive disease was defined as a FEV1/FVC <70. Residual volume (RV) was considered normal if the value was <120%, mild-abnormal if it was between 120% and 140%, moderate from 140% to 160%, and severe for values >160%. During follow-up and at the time of screening for HAPLO, the presence of lung infections was also recorded. Lung function score (LFS) was calculated as reported by Parimon et al. [4] and was developed as a score based on pretransplant FEV1 and DLCO to determine the extent of pulmonary compromise before transplant. A separate score was assigned to FEV1 and DLCO according to severity grades as previously described [4]. These scores were summed and then LFS was categorized according to the function score: category I (normal, score 2), category II (mildly decreased, score 3–4), category III (moderately decreased, score 5–6), and category IV (severely decreased, score 7–8).

Statistical analysis

Descriptive statistics were reported and compared using the Pearson's Chi-square test for categorical variables and the Wilcoxon's rank test for quantitative variables. Continuous variables were presented as median and range; categorical variables were reported as frequency and percentage. Linear mixed models were used to analyze PFTs at baseline, 100 days, and 1 year after HAPLO. Overall survival (OS) was calculated with the Kaplan–Meier method from the time of HAPLO to death. Relapse incidence, non-relapse mortality (NRM) and GVHD were calculated using the cumulative incidence estimates. Death was considered the competing event for relapse or GvHD, relapse was the competing event for NRM.

Tests of significance were two-tailed and considered significant at $p < 0.05$. All statistical analyses were performed using SPSS version 20.0 (SPSS, Chicago, IL) and R version 3.5.0 (R Institute for Statistical Computing, Vienna, Austria).

Results

Study population

The median follow-up was 32 (range: 12–74) months. The main patient- and transplant- related characteristics are shown in Table 1. Cytomegalovirus serology was positive in 45%, and 65% of patients were male.

Table 1. Patient and transplant characteristics.

Characteristics	Value
Age at HAPLO, median, range (years)	58 (16–73)
Gender	
Male	52 (65%)
Female	28 (35%)
BMI, median, range	23.6 (16–34.9)
Smoking	
Yes	23 (29%)
No	57 (71%)
DM	
Yes	6 (8%)
No	74 (92%)
Hypertension	
Yes	18 (23%)
No	62 (77%)
Lung infection at HAPLO	
Yes	3 (4%)
No	68 (85%)
missing	9 (11%)
Diagnosis	
AML	41 (51%)
ALL	10 (13%)
Lymphoma	14 (18%)
MM	2 (3%)
MDS	9 (10%)
MPD	4 (5%)
ECOG	
0	50 (63%)
≥1	30 (37%)
HCT-CI, median, range	1 (0–6)
Disease status at HAPLO	
CR	49 (61%)
PR	10 (13%)
Progressive disease	17 (21%)
Untreated	4 (5%)
DRI	
Low–intermediate	60 (75%)
High–very high	20 (25%)
Year of HAPLO, median, range	2017 (2013–2019)
Graft source	
BM	7 (9%)
PBSC	73 (91%)
Conditioning regimen	
Reduced	32 (40%)
Myeloablative	19 (24%)
Sequential	29 (36%)
PTCY	
Days 3 + 4	7 (9%)
Days 3 + 5	64 (80%)
Day 3 only	9 (11%)

HAPLO: haploidentical transplantation; BMI: body mass index; DM: diabetes mellitus; AML: acute myeloid leukemia; ALL: acute lymphoblastic leukemia; MM: multiple myeloma; MDS: myelodysplastic syndrome; MPD: myeloproliferative disease; ECOG: Eastern Cooperative Oncology Group; HCT-CI: hematopoietic cell transplantation comorbidity index; CR: complete remission; PR: partial remission; DRI: disease risk index; BM: bone marrow; PBSC: peripheral blood stem cells; PTCY: post-transplant cyclophosphamide.

The median age was 58 (range: 16–73) years. The proportion of surviving patients with available PFT at 100 days and 1 year was 86% and 68%, respectively. Diagnosis was acute myeloid leukemia (AML) in 51% ($n = 41$) and DRI was intermediate-low in 75% ($n = 60$) of the cases. Disease status before HAPLO was complete remission in 61% ($n = 49$). Graft source was PBSC in 91% ($n = 73$) of the cases. A RIC regimen was given to 40% ($n = 32$) of the patients and the most frequent chemotherapy regimen was thiotepa, busulfan and fludarabine in 61% ($n = 49$). GvHD prophylaxis consisted of Cyclosporine A and MMF in all but one patient who received methotrexate in place of MMF. All patients received PTCY, 64 (80%) at days +3 and +5 after HAPLO, 7 (9%) at days +3 and +4, and 9 (11%) only at day +3. Seventy-three (91%) patients received ATG.

In total, 29% of the patients had previously smoked or were smokers, 8% had type 2 diabetes, and 23% suffered from hypertension. At screening for HAPLO, five (6%) patients had restrictive lung disease, nine (11%) met the criteria for obstructive lung disease, and DLCOc was impaired in 74% of patients. Three patients were reported as having a lung infection, one of which was of bacterial origin and two were diagnosed as possibly aspergillosis. Table 2 summarizes PFT data before HAPLO, at 100 days, and 1 year after HAPLO. The median FEV1 was 100 (range: 58–146) before HAPLO, 93 (range: 42–10) at 100 days after HAPLO, and 99 (range: 32–144) at 1 year. The median FVC was 106 (range: 57–153), 98 (range: 44–148) and 106 (range: 31–153) at pre HSCT, 100 days and 1 year after HAPLO, respectively. FEV1 and FVC were significantly different over the 1 year follow up ($p = 0.01$ and $p = 0.001$, respectively). The median FEV1/FVC was 80 (range 51–105) before HAPLO, 77 (range: 54–103) after 100 days, and 75 (range: 43–100) after 1 year. FEV1/FVC, residual volume, and TLC remained stable from baseline to 1 year ($p = 0.27$, $p = 0.84$ and $p = 0.21$, respectively). In contrast, DLCOc remained impaired during the follow-up period ($p < 0.001$). The median DLCOc was 72 (range: 39–105), 64 (range: 16–105) and 66 (range: 26–104) at baseline, 100 days and 1 year after HAPLO.

Table 2. PFT parameters at baseline (before HAPLO), at 100 days and at 1 year.

PFT parameters, median (range)	Baseline	100 days	1 year	*p* Value
FEV1	100 (58–146)	93 (42–140)	99 (32–144)	0.01
FVC	106 (57–153)	98 (44–148)	106 (31–153)	0.001
FEV1/FVC	77.9 (51.6–105)	77 (54–103)	75 (43–100)	0.27
RV	88 (45–140)	86.9 (36–214.29)	92.5 (46.9–181)	0.84
TLC	100 (65–134)	95.7 (53–148)	100 (45–124)	0.21
DLCOc	71.7 (39–105–79)	64 (15.69–105)	66.1 (26–104)	<0.001

PFT: pulmonary function test; HAPLO: haploidentical stem cell transplantation; FEV1: forced expiratory volume in 1 s; FVC: forced vital capacity; FEV1/FVC: ratio of forced expiratory volume in 1 s / forced vital capacity; RV: residual volume; TLC: total lung capacity; DLCOc; diffusing capacity of lungs for carbon monoxide corrected for hemoglobin concentration.

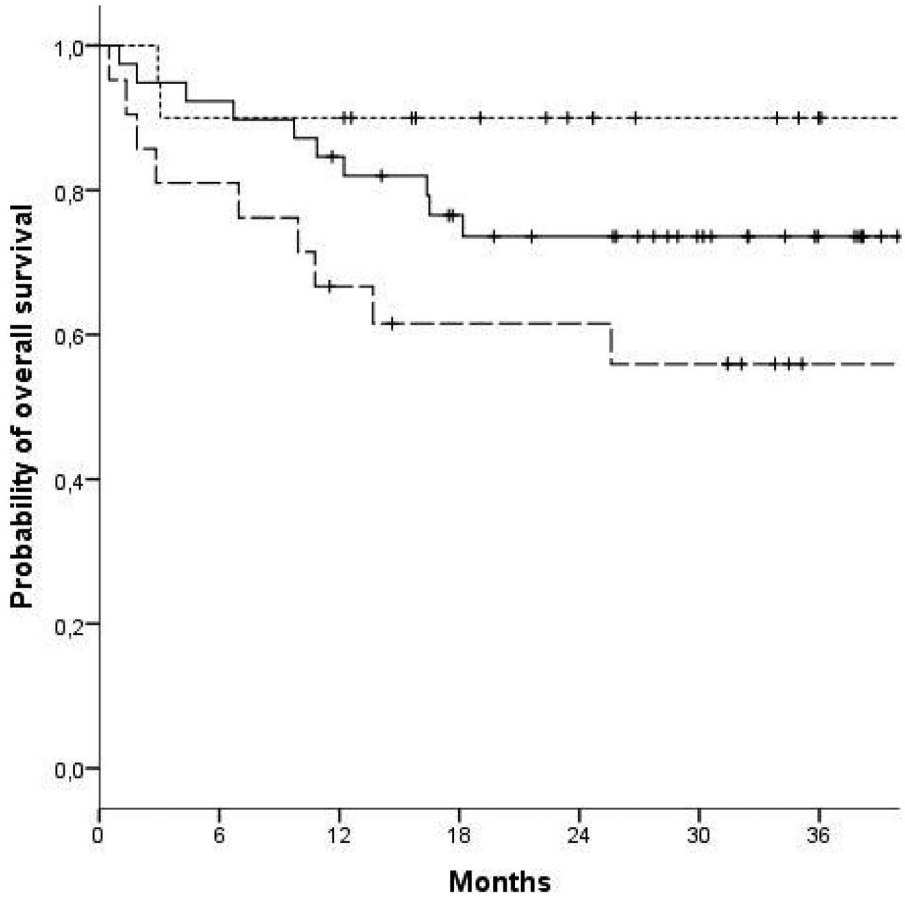

Figure 1. Overall survival at 2 years according to lung function score. The dotted line represents category I, the continuous line represents category II, and the dashed line represents categories III and IV.

Twenty-nine patients had a respiratory infection during the follow-up period. Of these, 19 were bacterial, three were viral, and two were of fungal origin; five had no microbial documentation. During the 1-year follow-up period, four patients met the criteria for bronchiolitis obliterans syndrome (BOS) and two for interstitial lung disease. Of these, only one had died at last follow-up.

GvHD, relapse incidence, NRM and OS

The cumulative incidence of grade II–IV acute GvHD was 21% (95% CI 14–33%). At 2 years, the cumulative incidence of chronic GvHD was 24% (95% CI 18–39%). Non-relapse mortality was 9% (95% CI 4–18%) at 100 days, and 14% (95% CI 8–24%) at 2 years. Relapse incidence was 3% (95% CI 1–10%) and 14% (95% CI 8–24%) at 100 days and 2 years, respectively.

Overall survival at 2 years was 73% (95% CI 62–82%). Patients with an abnormal pre-transplant DLCOc (<80%) had a trend toward an inferior OS (69% versus 91%, $p = 0.05$).

In all, 22 patients died. The cause of death was relapse of hematological disease in seven (35%), infection in seven (35%), GvHD in two (9%), multi-organ failure in four (20%), and missing in two.

Pre-transplant predictors for impaired DLCO and lung function score validation

Recipients with impaired DLCO at transplant were more frequently transplanted before 2017 ($p = 0.03$). No differences in the risk of having an impaired DLCO were found with respect to age, stem cell source, disease type, disease state, gender, smoking habit, or body mass index.

Patient LFS was categorized as normal ($n = 20$), mildly decreased ($n = 39$), moderately decreased ($n = 17$) or severely decreased ($n = 4$). Due to the small number of patients with a severely decreased LFS, the last two categories were summated. The 2-year OS was 90% (95% CI 69–97%), 74% (95% CI 59–85%) and 62% (95% CI 42–79%) for LFS categories I, II and III–IV, respectively ($p = 0.03$) (Figure 1).

Discussion

We report a stable pulmonary function and a low rate of noninfectious pulmonary complications including interstitial and obstructive lung disease in patients undergoing HAPLO with PTCY in a single center. It has been widely demonstrated that pulmonary complications are a major cause of morbidity and mortality in the first year after transplant [15]. Underdiagnosed pulmonary complications were the most common cause of death found at postmortem in a series of 39 consecutive patients [16]. This finding emphasizes the importance of an appropriate follow-up for potentially treatable pulmonary complications in the post-transplant setting.

Previous data have suggested a possible protective role of ATG in reducing the risk of developing lung complications after HSCT [17]. Pulmonary function decline within 100 days after HSCT has been reported as being associated with development of chronic GvHD at 1 year [18]. In our cohort, most patients received ATG (except 9 who did not because of comorbidities); therefore, we were not able to explore this finding further by comparing the two groups.

A randomized trial conducted in patients undergoing unrelated donor HSCT reported that FEV1 and FVC remained stable in patients in the ATG arm while there was a significant decrease in the non-ATG arm [19]. We confirmed this finding with a low incidence of chronic GvHD at 2 years and only 4 cases of BOS in our cohort. It might be that ATG exerts a protective role in pulmonary tissue through its ability to reduce overall GvHD. However, the limited number of patients prevents us from drawing firm conclusions in this setting.

We report a relatively moderate number of pulmonary infections which is in line with that previously described in this setting [20,21], although we focused only on reporting respiratory tract infections.

We observed a significantly decreased DLCOc at baseline that remained impaired at 100 days and 1 year after HAPLO, but with a substantial stable pulmonary function during the follow-up period of 1 year. Other authors have reported an impaired DLCO in the related and unrelated setting [6,22–24]. One could speculate that an impaired DLCO at baseline could be due to infections or chemotherapy toxicities due to prior treatments. The impact of baseline DLCO on outcome is controversial. The interpretation of a reduced DLCO is frequently unclear, but may reflect the physiologic fitness of an individual; hence, it is included in the pre-transplant assessment by the hematopoietic cell transplantation comorbidity index (HCT-CI) [25]. Crawford et al. reported that a DLCO of less than 80% had a greatest risk of mortality [26]. Furthermore, the follow-up study of this cohort found that a reduced DLCO of less than 70% was an independent risk factor for the development of severe hepatic veno-occlusive disease, suggesting that a reduced DLCO may reflect systemic endothelial cell damage [27]. Parimon et al. [4] showed that a progressively worse DLCO was independently associated with an increase in the probability of early respiratory failure. However, a retrospective analysis on autologous and allogeneic recipients who received HCT with a DLCO of less than 60% reported no differences in NRM or respiratory failure when stratifying according to DLCO impairment, or by conditioning intensity for allogeneic HSCT. Interestingly, the majority of patients experienced an improvement in DLCO after 3 months [28]. In our study, we observed a decline in DLCOc at 100 days, which reverted at 1 year to the baseline. Patients with a DLCOc $<$80% had a trend toward inferior OS, but due to the small number of patients the effect did not reach statistical significance.

As it has been described, chronic GvHD and pre-HSCT pulmonary abnormality are the main determinants for the development of an impaired pulmonary function in long term survivors and chronic GvHD might be correlated with a restrictive pattern [24], confirming the possible link between the two. Thus, we can conclude that ATG also prevents the development of the interstitial pattern that we observed in only two cases. Identifying which patients are at greater risk in this setting would be an invaluable tool allowing treatment of the disease at a stage when it might be reversible. We observed a low rate of obstructive lung disease, diagnosed in four patients. This finding is in line with the reported incidence in a large retrospective cohort [29] even though the limited number of patients in our cohort prevent us from drawing conclusions.

Our study demonstrates that LFS can be successfully used for the assessment of transplant risk in patients undergoing HAPLO. LFS was proposed in patients undergoing HSCT with different haematological diseases [4]. Nevertheless, HAPLO was not represented as a graft source in these studies. In the current study, we confirm that LFS can stratify patients undergoing HAPLO in progressive risk categories with the mortality risk increasing from the low to the very high category. Despite our limited number of patients, and resultant reduction in statistical power of identifying differences between categories, LFS maintains its ability to predict survival outcomes in our cohort.

HSCT survivors have long-term changes in functional capacity, pulmonary function and quality of life. It has been recently reported that more active subjects showed better pulmonary function and functional capacity [30]. Therefore, early detection of pulmonary function changes after HAPLO may identify a subset of patients at the highest risk of subsequent pulmonary complications.

Our results suggest that PTCY does not have a negative effect on PFT in HAPLO recipients. These results should be further investigated in larger cohorts and with a longer follow-up, with the aim of more fully understanding reversible and/or long-term toxicities due to PTCY use in this setting.

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Disclosure statement

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ORCID

Annalisa Paviglianiti http://orcid.org/0000-0002-4243-9252
Mara Memoli http://orcid.org/0000-0002-1922-6048

References

[1] Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. N Engl J Med. 2010;363(22):2091–2101.
[2] Passweg JR, Baldomero H, Chabannon C, for the European Society for Blood and Marrow Transplantation (EBMT), et al. The EBMT activity survey on hematopoietic-cell transplantation and cellular therapy 2018: CAR-T's come into focus. Bone Marrow Transplant. 2020;55(8):1604–1613.
[3] Yen KT, Lee AS, Krowka MJ, et al. Pulmonary complications in bone marrow transplantation: a practical approach to diagnosis and treatment. Clin Chest Med. 2004;25(1):189–201.
[4] Parimon T, Madtes DK, Au DH, et al. Pretransplant lung function, respiratory failure, and mortality after stem cell transplantation. Am J Respir Crit Care Med. 2005;172(3):384–390.
[5] Badier M, Guillot C, Delpierre S, et al. Pulmonary function changes 100 days and one year after bone marrow transplantation. Bone Marrow Transplant. 1993;12(5):457–461.
[6] Dirou S, Malard F, Chambellan A, et al. Stable long-term pulmonary function after fludarabine, antithymocyte globulin and i.v. BU for reduced-intensity conditioning allogeneic SCT. Bone Marrow Transplant. 2014;49(5):622–627.
[7] Piñana JL, Martino R, Barba P, et al. Pulmonary function testing prior to reduced intensity conditioning allogeneic stem cell transplantation in an unselected patient cohort predicts posttransplantation pulmonary complications and outcome. Am J Hematol. 2012;87(1):9–14.
[8] Sagou K, Ukai S, Adachi Y, et al. Decline of forced expiratory volume in 1 s after allogeneic hematopoietic cell transplantation is a good indicator for pulmonary damage and is associated with busulfan use. Int J Hematol. 2019;109(3):299–308.
[9] Lee J-H, Choi S-J, Lee J-H, et al. Severe metabolic abnormalities after allogeneic hematopoietic cell transplantation. Bone Marrow Transplant. 2005;35(1):63–69.
[10] Ramirez-Sarmiento A, Orozco-Levi M, Walter EC, et al. Influence of pretransplantation restrictive lung disease on allogeneic hematopoietic cell transplantation outcomes. *Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2010;16(2):199–206.
[11] Ahn JH, Jo K-W, Song JW, et al. Prognostic role of FEV1 for survival in bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation. Clin Transplant. 2015;29(12):1133–1139.
[12] Srinivasan A, Sunkara A, Mitchell W, et al. Recovery of pulmonary function after allogeneic hematopoietic cell transplantation in children is associated with improved survival. Biol Blood Marrow Transplant. 2017;23(12):2102–2109.
[13] Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. Biol Blood Marrow Transplant. 2009;15(12):1628–1633.
[14] Armand P, Kim HT, Logan BR, et al. Validation and refinement of the Disease Risk Index for allogeneic stem cell transplantation. Blood. 2014;123(23):3664–3671.
[15] Lucena CM, Torres A, Rovira M, et al. Pulmonary complications in hematopoietic SCT: a prospective study. Bone Marrow Transplant. 2014;49(10):1293–1299.
[16] Sharma S, Nadrous HF, Peters SG, et al. Pulmonary complications in adult blood and marrow transplant recipients: autopsy findings. Chest. 2005;128(3):1385–1392.
[17] Ditschkowski M, Elmaagacli AH, Trenschel R, et al. T-cell depletion prevents from bronchiolitis obliterans and bronchiolitis obliterans with organizing pneumonia after allogeneic hematopoietic stem cell

transplantation with related donors. Haematologica. 2007;92(4):558–561.

[18] Walter EC, Orozco-Levi M, Ramirez-Sarmiento A, et al. Lung function and long-term complications after allogeneic hematopoietic cell transplant. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2010;16(1):53–61.

[19] Bacigalupo A, Lamparelli T, Barisione G, Gruppo Italiano Trapianti Midollo Osseo (GITMO), et al. Thymoglobulin prevents chronic graft-versus-host disease, chronic lung dysfunction, and late transplant-related mortality: long-term follow-up of a randomized trial in patients undergoing unrelated donor transplantation. Biol Blood Marrow Transplant. 2006; 12(5):560–565.

[20] Slade M, Goldsmith S, Romee R, et al. Epidemiology of infections following haploidentical peripheral blood hematopoietic cell transplantation. Transpl Infect Dis Off J Transplant Soc. 2017;19:e12629.

[21] Mohty R, Brissot E, Battipaglia G, et al. Infectious complications after post-transplantation cyclophosphamide and anti-thymocyte globulin-based haploidentical stem cell transplantation. Br J Haematol. 2019;187(3):e64–e68.

[22] Chien JW, Maris MB, Sandmaier BM, et al. Comparison of lung function after myeloablative and 2 Gy of total body irradiation-based regimens for hematopoietic stem cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2005; 11(4):288–296.

[23] White AC, Terrin N, Miller KB, et al. Impaired respiratory and skeletal muscle strength in patients prior to hematopoietic stem-cell transplantation. Chest. 2005; 128(1):145–152.

[24] Savani BN, Montero A, Srinivasan R, et al. Chronic GVHD and pretransplantation abnormalities in pulmonary function are the main determinants predicting worsening pulmonary function in long-term survivors after stem cell transplantation. Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2006;12(12):1261–1269.

[25] Sorror ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. Blood. 2005;106(8):2912–2919.

[26] Crawford SW, Fisher L. Predictive value of pulmonary function tests before marrow transplantation. Chest. 1992;101(5):1257–1264.

[27] Matute-Bello G, McDonald GD, Hinds MS, et al. Association of pulmonary function testing abnormalities and severe veno-occlusive disease of the liver after marrow transplantation. Bone Marrow Transplant. 1998;21(11):1125–1130.

[28] Chien JW, Sullivan KM. Carbon monoxide diffusion capacity: how low can you go for hematopoietic cell transplantation eligibility? Biol Blood Marrow Transplant J Am Soc Blood Marrow Transplant. 2009; 15(4):447–453.

[29] Vieira AG, Funke VAM, Nunes EC, et al. Bronchiolitis obliterans in patients undergoing allogeneic hematopoietic SCT. Bone Marrow Transplant. 2014;49(6): 812–817.

[30] Penna GB, da Silva TC, Aparecida Paz A, et al. Functional capacity, pulmonary function, and quality of life in hematopoietic stem cell transplantation survivors. Support. Care cancer Off. J. Multinatl. Assoc. Supportive Care in Cancer 2021(29):4015–4021.